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ORIGINAL ARTICLE

Effect of Combining Ultralow-dose Naloxone with Morphine in Intravenous Patient-controlled Analgesia: The Cut-off Ratio of Naloxone to Morphine for Antiemesis After Gynecologic Surgery

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Background/Purpose: Admixing an ultralow dose of naloxone with intravenous morphine patient-controlled analgesia (PCA) has been shown to decrease postoperative nausea. However, the cut-off ratio of the naloxone-morphine admixture for antiemetic effects has not been investigated. The purpose of this study was to investigate the cut-off ratio of naloxone-morphine admixture in PCA for antiemesis after gynecologic surgery.
Methods: This double-blind study enrolled 120 female patients who were scheduled for gynecologic surgery under general anesthesia. Patients were randomly allocated to one of three groups ($n = 40$ for each group). The concentration of naloxone and morphine respectively was 0 μg/mL and 1 mg/mL in group 1, 0.1 μg/mL and 1 mg/mL in group 2 (1:10,000), and 1 μg/mL and 1 mg/mL in group 3 (1:1000). Morphine consumption, verbal rating score of wound pain at rest and with exertion, and morphine-related side effects were investigated at 1, 2, 4 and 24 hours postoperatively.
Results: A total of 112 patients completed the study (37 in group 1, 36 in group 2, 39 in group 3). The incidence of nausea during the postoperative 4–24 hours was significantly lower in group 3 than in group 1 (23.1% *vs.* 56.8%, $p < 0.05$). Furthermore, the overall incidence of severe nausea was significantly lower in group 3 than in group 1 (2.6% *vs.* 24.3%, $p < 0.05$) as was the rescue antiemetic requirements (5.1% *vs.* 24.3%, $p < 0.05$). However, there were no significant differences between groups 2 and 1. The pain scores (at rest and with exertion) and 24-hour morphine consumption were not significantly different among the three groups.
Conclusion: The antiemetic efficacy of ultralow-dose naloxone combined with PCA morphine is limited by a cut-off ratio of naloxone to morphine of 1:10,000. [*J Formos Med Assoc* 2008;107(6):478–484]

Key Words: opioid antagonists, patient-controlled analgesia, postoperative nausea and vomiting

The use of morphine in intravenous patient-controlled analgesia (PCA) is frequently associated with side effects such as nausea and vomiting. Various agents, such as butyrophenones,[1] phenothiazines,[2] antihistamines,[3] and nonsteroidal anti-inflammatory drugs[4] have been added to opioids to reduce postoperative PCA-related side effects. In a 1997 study, Gan et al revealed that low-dose infusion of naloxone with PCA morphine not only decreased opioid side effects but also

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Received: January 15, 2007
Revised: March 13, 2007
Accepted: June 5, 2007

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improved analgesia.[5] Clinically, it is not convenient to use an infusion pump with a PCA machine. Therefore, combination of low-dose naloxone and morphine in intravenous postoperative PCA has been investigated as a more convenient method. The results of naloxone-morphine combinations were initially disappointing. Sartain et al found that combining naloxone (26.7 μg/mL) and morphine (2 mg/mL) did not have any benefit.[6] Cepeda et al found that addition of low-dose naloxone (6 μg/mL) with morphine (1 mg/mL) did not decrease the incidence of opioid side effects.[7] In a later study, Cepeda et al[8] found that addition of ultralow-dose naloxone (0.6 μg/mL) with morphine (1 mg/mL) did not affect analgesia and the opioid requirement but decreased the incidence of opioid side effects. However, no study has investigated the antiemetic effects of lower ratios of the naloxone-morphine admixture. The purpose of this study was to investigate the cut-off ratio of the naloxone-morphine admixture in PCA for antiemesis after gynecologic surgery.

Materials and Methods

Patients

This randomized, double-blind, placebo-controlled study was approved by the Hospital Committee for Human Investigation. Written informed consent was obtained from all patients. A total of 120 Taiwanese women (18–66 years, ASA physical status of I or II) scheduled for elective total abdominal hysterectomy under general anesthesia and postoperative analgesia with a PCA device were assessed for inclusion in the study. Patients with known morphine allergy or who received opioids or any antiemetics within 7 days of the study were excluded.

Randomization and blinding

A specially trained nurse anesthetist, not involved in any subsequent assessments, was in charge of the study medication preparation and group assignment. According to a computer-generated random number table, patients were allocated to one of three groups ($n = 40$ per group). The control group (group 1) received morphine 1 mg/mL alone. The two treatment groups each received a naloxone-morphine admixture with a ratio of naloxone to morphine of 1:10,000 or 1:1,000 (groups 2 and 3, respectively). The study solutions were diluted in saline to produce equal volumes to ensure proper blinding. The two naloxone-morphine admixtures were prepared by mixing 0.01 and 0.1 mg of naloxone (groups 2 and 3, respectively) with 100 mg of morphine in 0.9% saline to a total volume of 100 mL. The study was double-blinded, with the patient, the patient's family, anesthesiologist, nursing staff, and evaluators all unaware of the randomization.

Rationale for the naloxone-morphine admixture ratios

The rationale for the concentration of naloxone in group 3 was based on the average amount of morphine required in our previous study in a similar population.[3] We estimated that if we used a ratio of naloxone to morphine of 1:1000, the dose of naloxone a patient would receive would be approximately 0.065 μg/kg/hr in the first 4 hours when the PCA requirements are the highest, and 0.012 μg/kg/hr afterwards. These naloxone doses are similar to the ultralow doses that have been reported to augment opioid effects in animal models,[9,10] and are very close to the ultralow doses of naloxone that have been proven to be effective in reducing opioid side effects while preserving the adequacy of pain management.[8] Moreover, 10% of this ratio was chosen for group 2 (1:10,000) to disclose whether a minimal naloxone concentration would still be potent enough to reduce morphine-induced emesis.

Anesthesia

Before the surgery, all patients were instructed on the operational use of the PCA system and a 0–10 visual analog scale (VAS), where 0 represented no pain and 10 the worst pain imaginable. All patients fasted at least 8 hours before surgery. A standard general anesthetic was given, comprising thiopental 3–5 mg/kg, fentanyl 1.5–3 μg/kg,

and atracurium 0.5–0.8 mg/kg. Anesthesia was maintained by isoflurane 0.8–1.5% in oxygen. The last dose of fentanyl had to be given 30 minutes prior to the end of the surgical procedure. Edrophonium 0.5–1 mg/kg and atropine 0.015 mg/kg were given to antagonize residual neuromuscular block at the end of surgery.

Postoperative management

Postoperative analgesia was provided in the recovery room immediately after the patient complained of pain. At the discretion of the nursing staff or the attending anesthesiologist, the assigned PCA solution in 1- to 2-mL increments was administered to the patient until the patient was comfortable. When the patient was stable and sufficiently alert, PCA was initiated. One milliliter of PCA solution was administered on demand with a 5-minute lockout and no background infusion was set. Patients were continuously monitored with a three-lead electrocardiogram, digital pulse oximetry, and noninvasive blood pressure monitoring during their stay in the postoperative recovery room. After a 1-hour stay in the recovery room, patients were transferred to wards when their vital signs were stable.

Postoperative evaluation

Data obtained for each patient included age, weight, height, and duration of anesthesia. Assessments of pain, nausea, vomiting, pruritus, sedation, PCA morphine and rescue antiemetic and antipruritic requirements, as well as any noted side effects, were recorded by an independent clinical investigator at 1, 2, 4 and 24 hours postoperatively. Patients were instructed to report the intensity of pain at rest and with exertion (coughing and deep inspiration) using VAS and to use PCA to maintain a VAS ≤ 3. We asked patients to categorize the severity of nausea, vomiting and pruritus at the end of the study period as none, mild, moderate or severe. Nausea and vomiting was treated with intravenous prochlorperazine 10 mg; pruritus was treated with intravenous diphenhydramine 30 mg. The symptomatic treatments were repeated if necessary. The level of sedation was assessed by the investigator by using a 5-point scale (0 = fully awake; 1 = drowsy, closed eyes; 2 = asleep, easily aroused with light tactile stimulation or a simple verbal command; 3 = asleep, arousable only by strong physical stimulation; 4 = unarousable).[11] A sedation score ≥ 3 was regarded as unacceptable in this context and was to be assessed and reported by any healthcare personnel with the subject then being switched to an alternate analgesic modality. If respiratory depression occurred (respiratory rate < 8 breaths/min; $SaO_2 < 90\%$; sedation score ≥ 3), PCA was turned off and the patient given naloxone 40 μg intravenously. Urinary retention could not be assessed due to the routine use of indwelling catheters in all patients.

Statistical analysis

A series of one-way analyses of variance was conducted to examine differences among the three groups with respect to continuous variables. If a significant difference was found, Tukey's *post hoc* comparisons were used to detect the intergroup differences. The Kruskal-Wallis test was used to determine differences among the three groups with respect to ordinal variables, and *post hoc* comparisons between groups were made using the Mann-Whitney U test. Categorical variables were analyzed using 2×2 χ^2 tests to determine the differences between group 1 and group 2 and the differences between group 1 and group 3. All follow-up analyses were corrected for the number of simultaneous contrasts by using Bonferroni's adjustments. A p value < 0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled in the study over an 8-month period. Eight patients were subsequently excluded for a variety of reasons: one patient experienced a suspected antibiotic allergy during surgery; two patients were re-operated on within 24 hours of surgery for continuous hemorrhage; two patients had the PCA machine replaced

twice because of pump malfunction; and data collection was incomplete in three patients. Thus, 112 patients completed the study: 37 in group 1; 36 in group 2; and 39 in group 3. Patient demographic and intraoperative variables were comparable in all groups (Table 1).

Pain intensities at rest and with exertion at each of the observatory time points did not differ statistically among the groups (Figures 1 and 2), nor did morphine consumption (Figure 3). In the first 4 postoperative hours, when the morphine requirements were highest, patients in groups 2 and 3 respectively received average doses of naloxone that were 0.006 and 0.061 μg/kg/hr (taking the average patient's weight in the corresponding group), and then 0.001 and 0.008 μg/kg/hr afterwards for the following 4–24 hours. There was no report of inadequate analgesia, morphine-related respiratory depression or somnolence (sedation score ≥ 3).

The incidence and severity of nausea, vomiting, pruritus, and requests for rescue antiemetic and antipruritic medications are reported in Table 2. Compared with the control group, the overall (0–24 hour) incidence of nausea and vomiting was not significantly reduced in group 3. However, the incidence of nausea during the postoperative 4–24 hours was significantly lower in group 3 than in group 1 (23.1% *vs.* 56.8%, $p < 0.05$). Furthermore, the overall incidence of severe nausea was significantly lower in group 3 than in group 1 (2.6% *vs.* 24.3%, $p < 0.05$). The incidence of severe vomiting was also lower in group 3 than in group 1 (2.6% *vs.* 18.9%, $p = 0.054$); however, the difference was not statistically significant. The number of patients requiring prochlorperazine was also significantly less in group 3 than in group 1 (5.1% *vs.* 24.3%, $p < 0.05$). Additionally, the total number of doses of prochlorperazine was least in group 3. In contrast, there were no significant differences between group 2 and group 1 with regard to the incidence and severity of nausea and vomiting, and to the antiemetic requirements.

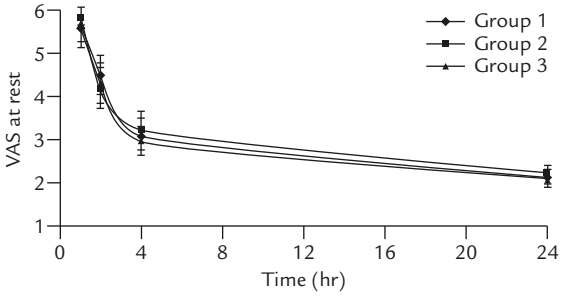

Figure 1. Visual analog scale (VAS) at rest (mean and 95% confidence intervals). There were no significant differences among groups. Group 1 = control group; Group 2 = 1:10,000 naloxone-morphine admixture group; Group 3 = 1:1000 naloxone-morphine admixture group.

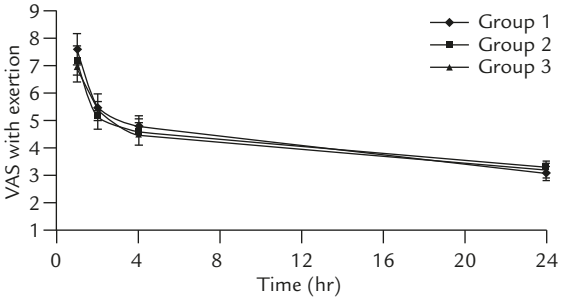

Figure 2. Visual analog scale (VAS) with exertion (mean and 95% confidence intervals). There were no significant differences among groups. Group 1 = control group; Group 2 = 1:10,000 naloxone-morphine admixture group; Group 3 = 1:1000 naloxone-morphine admixture group.

Table 1. Patient demographic and intraoperative data*†

	Group 1 ($n = 37$)	Group 2 ($n = 36$)	Group 3 ($n = 39$)
Age (yr)	44.8 (21–62)	44.5 (23–66)	45.7 (23–65)
ASA (I/II)	20/17	21/15	19/20
Height (cm)	157.0 ± 5.8	155.7 ± 4.8	156.1 ± 5.6
Weight (kg)	56.2 ± 8.2	56.8 ± 9.6	58.9 ± 9.8
Duration of anesthesia (min)	113 ± 42	125 ± 46	119 ± 39
Intraoperative fentanyl used (μg)	130.2 ± 36.7	129.1 ± 34.1	131.2 ± 38.1

**Data presented as mean (range), n or mean ± standard deviation; †the three groups were similar for all variables tested. Group 1 = control group; Group 2 = 1:10,000 naloxone-morphine admixture group; Group 3 = 1:1000 naloxone-morphine admixture group.*

The incidence and severity of pruritus were similar among the groups. Most patients experiencing pruritus reported pruritus as mild in severity. Two patients, one each from group 1 and 3, reported moderate pruritus and required diphenhydramine.

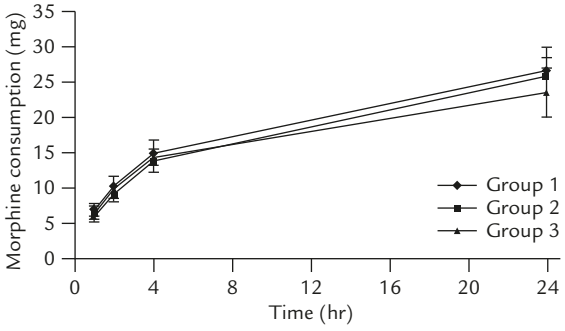

Figure 3. Morphine consumption (mean and 95% confidence intervals). There were no significant differences among groups. Group 1 = control group; Group 2 = 1:10,000 naloxone-morphine admixture group; Group 3 = 1:1000 naloxone-morphine admixture group.

Discussion

This study shows that the addition of naloxone to PCA morphine at a naloxone-to-morphine ratio of 1:1000 significantly reduces morphine-induced nausea and the need for further antiemetic treatment without affecting analgesia. A ratio of naloxone to morphine of 1:10,000 does not decrease the opioid side effects. The concentration-dependent efficacy demonstrates that the ratio of naloxone-morphine admixtures plays a critical role in the prophylaxis of PCA morphine-induced emesis.

The use of opioid antagonists to decrease opioid side effects while preserving opioid analgesia is an attractive concept. As opioid side effects and analgesia have different dose-response curves[5] and opioid side effects are attributable to activation of inhibitory mu opioid receptors (e.g. on interneurons),[5,12,13] the administration of small doses of opioid antagonists may be potentially

Table 2. Main adverse effects and rescue antiemetic and antipruritic requirements*

	Group 1 ($n=37$)	Group 2 ($n=36$)	Group 3 ($n=39$)
Nausea			
0–24 hr	26 (70.3)	25 (69.4)	19 (48.7)
Mild	8	8	12
Moderate	9	10	6
Severe	9 (24.3)	7 (19.4)	1 (2.6)†
0–4 hr	17 (45.9)	20 (55.6)	16 (41)
4–24 hr	21 (56.8)	17 (47.2)	9 (23.1)†
Vomiting			
0–24 hr	16 (43.2)	14 (38.9)	13 (33.3)
Mild	3	2	7
Moderate	6	6	5
Severe	7 (18.9)	6 (16.7)	1 (2.6)
0–4 hr	7 (18.9)	10 (27.8)	6 (15.4)
4–24 hr	13 (35.1)	10 (27.8)	7 (17.9)
Patients requiring prochlorperazine	9 (24.3)	8 (22.2)	2 (5.1)†
Total no. of doses	14	10	3
Pruritus	7 (18.9)	5 (13.9)	2 (5.1)
Patients requiring diphenhydramine	1	0	1
Sedation score ≥ 3	0	0	0
Respiratory depression	0	0	0

**Data presented as n (%) or n; †$p<0.05$, group 3 vs. group 1. Group 1 = control group; Group 2 = 1:10,000 naloxone-morphine admixture group; Group 3 = 1:1000 naloxone-morphine admixture group.*

beneficial to obtain this goal. Depending on the methods of administration (separate continuous infusion *vs.* mixed intermittent bolus) and the drug doses (low *vs.* ultralow) applied, the use of naloxone with intravenous PCA morphine was found to result in either beneficial,[5,8,14] adverse[7] or no effects.[6]

Although the success of naloxone in preventing morphine-induced side effects is consistently reported for studies in which naloxone was administered by continuous infusion,[5,14] a separate infusion is seen as inconvenient in clinical practice. Cepeda et al were the first to assess the applicability of adding naloxone to a morphine solution for PCA in male and female patients undergoing a range of surgical procedures.[7] No benefit in terms of opioid side effects was seen, and in fact, the study was not designed to detect this benefit. Whether or not adding naloxone decreases side effects, the naloxone-to-morphine ratio of 6:1000 in the study was not a helpful option because it reversed the analgesia. The lack of benefit from naloxone was similarly reported in the study by Sartain et al, in which a naloxone-to-morphine ratio of 13.3:1000 was employed for postoperative PCA in women undergoing hysterectomy.[6] Although they did not find naloxone at risk of reversing analgesia with this higher dose, neither could they find any antiemetic benefit from naloxone. The lack of a constant concentration of naloxone from intermittent administration by PCA has been suggested to be the reason why naloxone was ineffective in preventing morphine-induced side effects.[6,14]

In view of the analgesia reversal observed with the 6:1000 naloxone-morphine admixture,[7] Cepeda et al subsequently used a lower ratio (6:10,000) in their recent study[8] to investigate if the opioid analgesia enhancement of ultralow doses of naloxone in animal models[9,10,15] was also present in humans. With this ratio, they found that ultralow-dose naloxone did not affect analgesia or morphine requirements, but it decreased the incidence of nausea and pruritus during the 24-hour postoperative period.[8] Using methods similar to Cepeda et al, we combined two ultralow doses of naloxone with PCA morphine. With a naloxone-to-morphine ratio of 1:1000 in group 3, a decrease in nausea was observed during the postoperative 4–24 hours. Reductions in both the severity of nausea and request for rescue antiemesis were also evident. In accordance with the findings of Cepeda et al, we did not observe the paradoxical effect of naloxone enhancement of opioid analgesia nor the undesired effect of analgesia reversal. In the first 4 hours postoperatively, when the morphine requirements were highest, patients in group 3 received an average dose of naloxone of 0.06 μg/kg/hr, and then 0.008 μg/kg/hr in the following 4–24 hours. Similarly, these naloxone doses were very close to the doses of naloxone (0.009–0.05 μg/kg/hr) used in the recent Cepeda et al study.[8] In contrast, the antinausea benefits of naloxone were no longer demonstrable at the lower ratio of 1:10,000 in group 2. While the naloxone doses in group 2 (0.001–0.006 μg/kg/hr), as those in group 3, also mirrored the ultralow doses that have been reported to augment opioid effects in mice (0.001–0.1 μg/kg),[9,10,15] neither analgesic enhancement nor an antiemetic effect was evident in our study at this dose. We believe that patients in group 2 received less than an effective dose of naloxone to prevent nausea.

The antinausea efficacy of naloxone in group 3 was apparent during the 4–24 hours postoperatively. The incidence of nausea in the first 4 hours was generally high among the groups. More than 65–84% of the patients experiencing nausea during the 24 hours postoperatively reported nausea within the first 4 hours. The lack of antiemetic benefits from naloxone in the first 4 hours was likely to be due to a combination of residual anesthetic effects in the immediate postoperative period, the nature of the surgical procedures, and patients being at high risk of postoperative nausea (e.g. women undergoing abdominal hysterectomy). As multiple antiemetic combinations for postoperative nausea and vomiting prophylaxis have shown promising results,[16,17] other antiemetics may be employed as comedication drugs in combination with ultralow doses of naloxone to exert a more powerful effect against PCA opioid-induced

emesis. In terms of antipruritic efficacy, naloxone has been shown to be effective against PCA opioid-induced pruritus.[8,14] In our study, the overall incidence of pruritus was higher in group 1 than in group 3 (18.9 *vs.* 5.1%, $p=0.16$). However, our sample size was too small to detect a statistical difference in the incidence of pruritus.

Another concern with the use of the naloxone-morphine admixture is the potential incompatibility of this combination. Although chemical compatibility data between naloxone and morphine are lacking, in two published studies, naloxone was shown to have clinical activity when similarly combined with morphine.[8,18]

In conclusion, addition of an ultralow dose of naloxone to PCA morphine at a naloxone-to-morphine ratio of 1:1000, but not 1:10,000, significantly reduced morphine-induced nausea and the need for further antiemetic treatment without affecting analgesia. The antiemetic efficacy of ultralow-dose naloxone combined with PCA morphine is therefore limited by a cut-off ratio of naloxone to morphine of 1:10,000. However, the optimal ratio of naloxone-morphine admixture for the prophylaxis of PCA morphine-induced side effects still needs to be evaluated in future studies.

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